Docking of DNA Duplexes on a Gold Surface

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Abstract

Understanding the interaction of DNA molecules with hard substrates is a crucial step both for the study of DNA and for the development of new nanotechnology applications, as the adsorption on hard surfaces strongly influences the shape and properties of DNA itself. We developed a multi-scale approach based on electronic structure calculations and molecular simulations, able to investigate the interaction of DNA molecules with a hard inorganic surface and to describe the adsorption configurations. Here we present our approach and we discuss preliminary results obtained with docking calculations of the adsorption of DNA molecules on Au(111). We obtained two main adsorption configurations, with DNA oligomers adsorbed parallel

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or tilted with respect to the surface. Our results evidence the importance of an accurate description of Lennard-Jones interactions between nucleobases and gold atoms in the DNA adsorption process.

1 Introduction

The orientation, the folding state and the functional properties of an individual DNA molecule when it is deposited on a hard inorganic surface are unknown, while they are crucial determinants for nanotechnology applications of nucleic acids, which span from electronics to health care. In the absence of experimental approaches that are able to resolve the three-dimensional atomic structure of the target system, a computational solution of the problem is particularly valuable. We have developed a multi-scale multi-step methodology based on electronic structure calculations and molecular simulations. Here, we report the principles of the general strategy and results on docking orientations of DNA molecules with different sequences on the Au(111) surface. This work is related to recent studies to assess atomistic computational methods for unraveling crucial features linked to the geometry and to the electronic structure [1–6].

Knowledge of the structure of DNA molecules on a hard substrate is extremely important to determine their ability to conduct charges in setups relevant for nanotechnologies, because the electronic structure and transfer rates are utterly sensitive to the conformational details [7–10]. It is known that the height of double-stranded DNA (dsDNA) molecules deposited horizontally on a hard substrate, measured by AFM, is about 50% of the diameter in solution [11, 12], which suggests possible unfolding of the nucleic acid in such experimental conditions, and consequent rupture of the intrinsic electron transfer functionality. However, no confirmation of this hypothesis exists. This knowledge is not accessible through conventional methods for the determination of the three-dimensional atomic structure of biological molecules, such as X-ray or NMR, which are hard to apply to the substrate environment. Classical Molecular Dynamics (MD) atomistic simulations are in principle the method of choice for a computational approach.

They have successfully been employed to describe the unfolding of biological molecules in solution [13–16]. However, the crucial point in any classical MD methodology is the parametric force field (FF), which is the potential energy necessary for the evolution of the atomic coordinates in time according to Newton's equations [17, 18]. Reliable force fields exist for liquid, solid and molecular materials, but the parametric description of the interaction

between molecules (especially macromolecules) and hard inorganic surfaces is still in its infancy [19]. We have developed force fields for the interaction of proteins with the Au(111) surface [20, 21] and we have reviewed our computational approach in this context, as well as similar efforts by other groups [22, 23]. We have recently extended this approach to the interaction of nucleic acid bases with the Au(111) surface [24–26], which requires specific parametrization due to the different functional groups and heterocycles of the bases. All-atom MD methods are computationally demanding and simulation lengths are limited to the microsecond time scale, while experimental studies often give the averaged behavior of a system over milliseconds or longer. For instance, all-atom MD simulations cannot be used to exhaustively investigate the approach of a DNA molecule to a surface, because the characteristic time scale of this process is too long. To tackle this process, it is necessary to freeze degrees of freedom. The most natural choice is to treat the solvent implicitly, as a continuous medium, and to constrain the internal degrees of freedom, so that the approaching molecule is reduced to a rigid body that can translate and rotate according to Brownian Dynamics (BD) equations [27]. Docking algorithms, with the newly parametrized interface FFs, allow us to find representative structures of the DNA@Au(111) complexes, which may then be refined by all-atom MD.

2 Method

Docking is a method that predicts the preferred orientation of two molecules in a binding or encounter complex. In the case of DNA on Au(111), the encounter complex is formed between a molecule and a surface. We can characterize the docking by the distance between the center of mass of the DNA and the surface and record the configurations of complexes that satisfy a defined adsorption distance criterion. In the present work, we are interested in the initial DNA-surface diffusional encounter and therefore, we treat the DNA molecule as rigid. In this approach the molecule moves in the solvent environment following Brownian Dynamics equations of motion, driven by the interaction with the surface.

2.1 ProMetCS

Different implicit models have been developed for simulations of molecules in solutions [27], but often they are not suitable for describing the interaction of a molecule with a surface [19, 28]. Moreover, different surfaces were

found to behave in qualitatively different ways as regards the adsorption of molecules (e.g. on metals, a barrier is formed by the energetically unfavored displacement of the water molecules) [29]. This means that a specific model should be developed for the Au(111) surface and it should account for the microscopic processes at the molecule-surface interface. For this reason, we used the ProMetCS [30], where the solvent behavior at the interface has been modeled implicitly including gold-specific desolvation terms and image-charge electrostatic terms.

ProMetCS was originally developed for protein-surface interactions and has been successfully used on these systems [31, 32]; it is tested here for DNA-surface interactions. The DNA-surface free energy function is the sum of three separate contributions:

$$U = E_{LJ} + U_{EP} + U_{desolv} \tag{1}$$

that are respectively Lennard-Jones (LJ) energy, electrostatic energy and desolvation energy.

The electrostatic interaction energy between the DNA molecule and the surface includes the effect of surface polarization using an image-charge model in continuum solvent and a correction for the surface desolvation at short regions. The desolvation energy contribution is dominated by the energy penalty of removing water from the metal and molecule surfaces, and is thus proportional to the DNA molecule and metal surface areas that are desolvated upon adsorption. Both the electrostatic and the desolvation terms are calculated here with the same methods developed for proteins, details can be found in the original ProMetCS work [30].

2.2 The LJ Interaction

While electrostatic and desolvation effects are calculated with general approximations suitable for a generic molecule adsorbed on a planar surface, the dispersion, repulsion and other short range electronic interactions between nucleobases and the surface are encoded in the atom-type dependent LJ parameters derived by us [24]. Our derivation was based on comparing the molecule-surface interaction energies and geometries in classical calculations to those of quantum calculations. Such benchmark calculations were performed with a particular care in the model for the description of long-range interaction between the molecules and the surface [33]. The force field parameterization is adopted here without modifications: the gold surface is modeled as in MD simulations [21], with three frozen layers of Au atoms in

the (111) triangular lattice and including polarization effects through virtual sites; the LJ parameters for Au atoms and for Au-DNA atom pairs are the same as in GolP [21]. LJ parameters for the interaction of backbone atoms with Au atoms are not specifically parameterized, they are evaluated by combining the amber99sb FF [34] and the GolP parameters for Au atoms via the standard Amber mixing rules. In docking simulations, the computation of the LJ interaction directly for each atom pair would be too cumbersome; therefore, the LJ interaction between the molecule and a single Au atom is saved on a three-dimensional grid encompassing the molecule with the origin placed at the molecule geometrical centre.

2.3 The Electrostatic Interaction

The adsorption of a double-stranded DNA molecule horizontally on a metallic surface in experiments can be performed in two ways: the surface is positively charged to attract the double stranded DNA [35], or the DNA molecule is adsorbed in two consecutive steps. In two-step protocols, DNA single strands are adsorbed on the surface in a solution with a high concentration of ions, and then the complementary strands are added in the solution. The high ionic concentration neutralizes the electrostatic repulsion between complementary strands, so that hybridization occurs and duplex DNA molecules are formed [36]. To be in line with the variety of experimental strategies, we decided to perform calculations both in high (500 mM) and low (10 mM) ionic strength (IS), and to deal with the charged surface only in case of need. In simulations performed at high ionic strength, DNA charges are screened by the implicit ions in solution only when the solvent is in between the molecule and the surface. When the molecule is 5 Å or less from gold, the solvent is supposed to be already displaced, neglecting the possibility of ions trapped between DNA and metal. To check the extent of this approximation we performed some tests in which we implicitly modeled the presence of counterions around backbone phosphate groups by halving the phosphate charges.

2.4 Clustering

A BD simulation yields a plethora of adsorption configurations, which can then be clustered into similarity groups, each characterized by a representative structure. Two clustering methods based on the root mean square deviations (RMSD) can be used to group the structures in genuinely different adsorption poses. The first approach is a single-linkage method that consists

in a bottom-up aggregation: a threshold RMSD value is defined and all the geometries within that value from the representative structure (defined as that with the lowest energy) are grouped together. The other approach consists of a top-down splitting (average-linkage clustering based on a reference structure) [37]: a number of final clusters is defined and the software groups all the configurations in such a way to reach that number. The second method has the obvious disadvantage that, if the requested number of clusters is too small, very different geometries can be grouped together; on the other hand the first method fails in grouping together very similar geometries that differ only for small rotations. Depending on the system under study, one or both the clustering algorithms were used to analyze the results.

2.5 Computational Approach

Rigid-body docking simulations were performed with the SDA software [38, 39]. The area of the Au(111) surface was 150×155 Å^2 and three atomic layers. DNA sequences were generated with the *x3dna* package [40]. We chose a standard length of 15 base pairs (bp) and uniform sequences poly(dG)-poly(dC) and poly(dA)-poly(dT), for which experimental characterization on gold exists [36]. Poly(dG)-poly(dC) [poly(dA)-poly(dT)] indicates the double-stranded oligomer with only guanine-cytosine (adenine-thymine) base pairs, with all the purines on the same strand. This choice of sequences allowed us to distinguish between the behavior of the four bases by comparing the adsorption energies and geometries of the two DNA molecules. The length of the DNA oligomers was chosen under the following considerations. In BD docking simulations, the internal degrees of freedom of the molecule are fixed. As a consequence, the molecule itself must be short enough to be suitable for the rigid body approximation. On the other hand, the molecule must be long enough that the effects of the different components of the energy (i.e. desolvation, LJ, electrostatic) be appreciable. Tests were performed also on a 8 bp and 20 bp sequences. The simulation box for DNA oligomers (without the space for the Au surface) is 20×20 Å and 50×50 Å in the x/y plane for the 8 bp and 15–20 bp, respectively; along the z axys initial distance of the molecule from the surface is 80 Å and 60 Å for 8 bp and 15–20 bp oligomers, respectively, and the orientation was chosen randomly. The simulation time step was 0.2 ps for the distance up to 30 Å from the surface to the DNA center and then was increased linearly within the next 10 Å up to 20 ps. The minimum distance of DNA atoms from the surface is 1.9 to 2.1 Å for tilted or vertical orientations (see Results and Discussion) and 2.6 to 2.7 Å for parallel orientation.

3 Results and Discussion

3.1 Validation of LJ Parameters and Choice of Target Systems

The first step of the study has been the assessment of tailored LJ parameters [24] for use in in the BD simulations, by verifying the agreement between BD simulations and MD simulations of the systems for which these parameters were originally derived, namely for individual bases on Au(111). A simple test, done excluding all the energy contributions except LJ and starting BD docking simulations with the single bases already adsorbed on the surface, allowed us to record the LJ interaction for comparison to MD values. As expected, the agreement between MD and BD is excellent (Table 1).

The choice of uniform sequences poly(dG)-poly(dC) and poly(dA)-poly(dT) allowed us to distinguish between the behavior of the four bases by comparing the adsorption energies and geometries of the two DNA molecules. The length (15 bp) of the DNA oligomers was chosen under consideration that in BD docking simulations the internal degrees of freedom of the molecule are frozen. As a consequence, the molecule itself must be short enough to be suitable for the rigid body approximation. On the other hand, the molecule must be long enough that the effects of the different components of the energy (i.e. desolvation, LJ, electrostatic) be appreciable.

The desolvation energy is a positive term that accounts for the unfavorable displacement of water molecules from a metal surface when the solute comes into contact [30]. This interaction is balanced by electrostatic and LJ interactions, which favor the adsorbed DNA configuration with respect to the desorbed one. The three contributions obviously depend on the geometry and length of the molecule. Before generating docking structures, we investigated whether the balance between the three energy components also depends on the molecule's length, which would make the results quite specific for the DNA length considered. To this aim, preliminary docking simulations

Table 1 Comparison of the LJ interaction energies between single configurations of the four nucleic acid bases and the Au(111) surface docked by BD and MD. Energies are given in kcal/mol

Base	BD	MD
cytosine	–14.4	–14.1
guanine	–19.3	–19.7
thymine	–14.7	–14.4
adenine	–17.8	–18.2

were performed, with poly(dA)-poly(dT) molecules of different lengths, with different orientations of the DNA axis relative to the surface and different distances of the DNA geometrical centre from the surface, so that the members of an individual cluster had a RMSD less than 5 Å.

The obtained adsorption configurations can be divided roughly in two groups: geometries with the molecule adsorbed parallel with respect to the surface and geometries with the molecule adsorbed tilted with respect to the surface. These two groups can be further divided depending on the rotation of the DNA molecule with respect to the surface, as discussed in the next subsection; here we focus on the orders of magnitude and trends of desolvation (Des) and LJ energies (Table 2).

The results in Table 2 illustrate that the ratio between Des and LJ energy values is similar through the different lengths, even if it is not constant because of the twisted shape of DNA. For the tilted configurations LJ is dominant with respect to desolvation, while for the parallel configurations the two energy components are very close to each other, with U_{desolv} always larger than U_{LJ}. The two components of the energy in the parallel adsorption geometries grow approximately linearly with the length of the helix, despite its twisted shape. These tests indicate that the length of the molecule does not substantially affect the LJ/Des ratio. We chose 15 bp as the optimal length: keeping the molecule as short as possible, with the aim of avoiding non-physical adsorption geometries due to the rigid body approximation, this length allows the molecule to touch the surface in three or four points in the parallel adsorption configuration, giving the opportunity to distinguish the behavior of purines and pyrimidines (i.e. the molecule can be rotated in a configuration with purines-pyrimidines-purines adsorbed on the surface or the opposite; the molecule can also adsorb

Table 2 Values of LJ and desolvation energies computed from BD docking simulations of DNA oligomers of different lengths and uniform sequence poly(dA)-poly(dT), adsorbed on Au(111) in parallel and tilted orientations relative to the surface. Each group is composed of approximately 10^6 structures and the energy values refer to the structure with the lowest total energy. Energies are in kcal/mol; the ratio is LJ/Des. The electrostatic interaction grows approximately linearly with the number of nucleotides that touch the surface: as a reference, the electrostatic interaction energy for the tilted 15 bp configuration is –9.1 kcal/mol

	Parallel			Tilted		
n Base Pairs	LJ	Des	Ratio	LJ	Des	Ratio
8	–22.5	26.7	–0.84	–75	45	–1.67
15	–44.5	46.8	–0.95	–79	45	–1.76
20	–60.5	67.6	–0.9	–85	52	–1.64

on the surface with four contact points, equally distributed between purines and pyrimidines).

3.2 Predicted Docking Configurations

The results reported in Table 3 are obtained with the two different clustering methods described in the Method section, depending on the simulation conditions. For simulations with IS = 10 mM, average-linkage clustering was used, as single-linkage method fails in grouping together parallel adsorption configurations that differ only for small rotations around the central axis that do not modify the docking orientation of the molecule. For simulations with IS = 500 mM, the single-linkage method was used, as the average-linkage clustering method failed to distinguish between the vertical configurations and the tilted ones that touch the surface with the purine strand. It is important to stress that, despite these ambiguities in the clustering process, the overall description of the system behavior (i.e. possible and preferred adsorption geometries) is the same from the two methods.

Figure 1 shows three distinguishable adsorption configurations that occur in the different simulation conditions: the DNA molecule is adsorbed parallel to the surface, tilted with respect to the surface or approximately vertical. The parallel and tilted geometries can be further grouped depending on the rotation of the molecule: the tilted DNA molecule can touch the surface with the purine or the pyrimidine strand; in a parallel adsorption geometry, the molecule

Table 3 Energies of the different adsorption geometries obtained at different ionic strength values for the DNA molecules with the two chosen sequences. ClSize is the relative population of the cluster with respect to the total, E-av is the average total energy of the cluster in kcal/mol

poly(dA)-poly(dT)				
	IS = 10 mM		IS = 500 mM	
Geometry	ClSize	E-av	ClSize	E-av
tilted A strand	62%	–33.9	27%	–16.5
tilted T strand	35%	–33.2	18%	–16.5
parallel A-T-A	3%	–32.5	–	–
vertical	–	–	55%	–13.1
poly(dG)-poly(dC)				
	IS = 10 mM		IS = 500 mM	
Geometry	ClSize	E-av	ClSize	E-av
tilted G strand	94%	–44.7	22%	–26.7
tilted C strand	4%	–36.2	10%	–27.2
parallel C-G-C	2%	–36.2	–	–
vertical	–	–	68%	–14.9

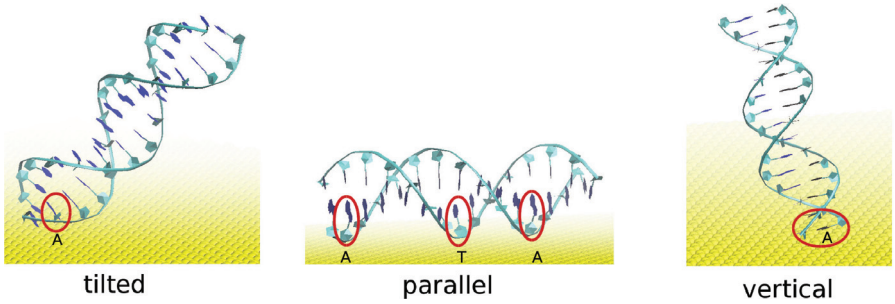

Figure 1 Possible docking configurations of a 15 bp poly(dA)-poly(dT) molecule on Au(111). Labels (A for adenine and T for thymine) highlight the nucleobase(s) closest to the surface.

touches the surface in three locations and therefore the final configuration can be either purine-pyrimidine-purine or the opposite, namely A-T-A (G-C-G) or T-A-T (C-G-C).

The results reported in Table 3 show that adsorption geometries are similar for the two sequences. At low ionic strength, the most populated cluster is the one with the DNA molecule tilted and the purine strand touching the surface, followed by the symmetric geometry, that is the tilted one with the pyrimidine strand adsorbed on gold. The molecule is adsorbed horizontally on the surface only at low ionic strength, while at high ionic concentration this geometry is substituted by the vertical adsorption orientation, which also becomes the most populated, due to the ionic screening of the electrostatic interaction disfavoring the backbone adsorption. When BD simulations are performed at high ionic concentration with half of the charge on DNA atoms, with the aim of mimicking the trapping of ions between the molecule and the surface, the results obtained for the geometries and energetics (not shown) are similar to those at IS = 500 mM: the molecules are adsorbed only in tilted and vertical geometries. By comparing the results at low and high ionic strength (with and without ions) we deduce that the electrostatic interaction between the molecule and the surface is determinant and favors the parallel adsorption of the molecule.

In the preliminary calculations done for choosing the length of the molecule, we already noticed that in the parallel adsorption configuration the desolvation and LJ interactions provide similar contributions to the total energy; thus, the contribution of electrostatics is crucial. Calculations done with a charged surface would surely change the balance between the populations of the different adsorption orientations, as the parallel configuration

would gain importance (for a positive surface) due to the increase of the electrostatic interaction. As we already mentioned, charging the metallic surface is one of the experimental techniques used for inducing DNA adsorption on metals and will be the subject of future studies.

It is interesting to note that DNA molecules may adsorb horizontally on the surface only in one of the two possible contact sequences: poly(dA)-poly(dT) prefers contacts A-T-A, poly(dG)-poly(dC) prefers contacts C-G-C. This outcome is in apparent contrast with DFT calculations, which predict the adsorption preference in the order G > A > C > T [24, 25]. One would intuitively expect the purine strand to touch the surface twice to maximize the interaction. Nevertheless, when the DNA molecule is adsorbed horizontally on the surface, the individual nucleobases are oriented perpendicularly with respect to gold, rotated differently depending on their position on the strand. The nucleobases energetic order for vertical adsorption is C > G > A > T. This explain our findings of A-T-A and C-G-C motifs: these are the conditions in which the nucleobase species that interacts the most with gold touches the surface twice. From these results it emerges that, even if it is the electrostatic interaction between the surface and the backbone that allows the parallel adsorption, the interaction between the internal bases and the surface is determinant for the final geometry. This is an encouraging result towards exploring the state of folding of DNA adsorbed on Au(111): these calculations suggest that the bases inside the helix interact with the surface despite the strong electrostatic influence of the backbone. This means that the folding can be affected by nucleobase-surface interactions.

For what concerns the tilted adsorption geometries, the energy difference between pyrimidine and purine strand adsorption configurations is very small, even if the cluster size points to a higher probability of the latter condition. It must not be forgotten that the rigid position of the molecule is an artifact of the rigid body approximation. Since this tilted configuration is the most frequent in the docking simulations, it will be interesting to adopt it as a starting geometry for MD simulations. In the MD simulation the molecule will be allowed to relax, and it will be possible to disclose if, even starting from a tilted configuration, it will evolve to a parallel orientation. This starting configuration could even favor an unfolding process since gold has direct access to the nucleobase core of DNA.

Finally, the vertical adsorption configuration is a consequence of the weaker interaction between the molecule and the surface at IS = 500 mM. This geometry is less interesting for what concerns the study of the behavior

of DNA on gold. Experimentally DNA molecules are usually adsorbed vertically within self-assembled monolayers using functional groups (thiols) for strengthening the molecule-surface bond. This docking vertical geometry is probably unstable for isolated non-functionalized molecules and it is not reproduced experimentally. Comparing the average energy values of the different adsorption geometries for the two DNA sequences, in particular for the parallel adsorption, we note that poly(dG)-poly(dC) interacts more strongly with the surface than poly(dA)-poly(dT). This difference can be attributed to the interaction of the bases with the surface, as the electrostatic interaction involves mainly the backbone, and is the same for the two sequences. This is a further evidence that nucleobase interaction with the surface influences the adsorption geometry of DNA oligomers, despite the strong effect of the charged backbone.

4 Conclusions

We performed docking calculations for two different 15-bp-long DNA oligomers adsorbing on Au(111), with sequences poly(dG)-poly(dC) and poly(dA)-poly(dT). We were able to obtain two main adsorption configurations, with the oligomer adsorbed parallel or tilted with respect to the surface. The interaction between purines and pyrimidines with gold, which has previously been parametrized on the basis of DFT calculations, determines the preferred adsorption orientation of the oligomer, dependent on the DNA sequence and ion concentration.

The calculations presented here are the first cases of DNA-surface docking and are mainly meant to illustrate the potential and usefulness of such approach. Yet, some computational aspects require further tests and refinements: specific gold-DNA LJ parameters have been obtained for the nucleobases but not for the DNA backbone; inclusion of counterions at the gold-DNA interface has been performed with a physically sound but somewhat qualitative approach; only two DNA sequences have been considered. Nevertheless, the fact that the same configurations are obtained through all the different calculations for these short sequences, together with the fact that the obtained geometries are the most intuitive when dealing with the simple shape of the DNA molecule, makes the present results sound and promising for future investigations. Eventually, they provide a clear evidence of the fact that the base-surface interaction coded in the LJ terms of our model plays an important role in the adsorption process, even when the helix is still folded.

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Biographies

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